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Primary biliary cirrhosis: an epidemiological study

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Summary and conclusions

A three-year study (1977-9) of primary biliary cirrhosis in the city of Sheffield disclosed 34 cases, a point prevalence of 54 per million population. Closer inspection showed an apparent clustering of cases, and the prevalence in relation to one water reservoir appeared to be more than ten times that of the other reservoirs. Nevertheless, analyses of the water showed no significant relevant differences between the reservoir serving areas with a high prevalence of cirrhosis and other reservoirs.

Despite the inconclusive results of the water analyses, these findings do suggest that an environmental agent may be a cause of primary biliary cirrhosis and that further epidemiological studies may help to elucidate the cause.

Introduction

Primary biliary cirrhosis is a rare disorder of unknown cause. Although large series of patients with the disease have been reported,[1 2] these have come from major referral centres and have been based on the experience of many years. Little information, however, has been published on the epidemiology of this disease. This paper reports a study on the prevalence of the disorder in the city of Sheffield and also examines factors which may contribute to the cause of primary biliary cirrhosis.

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Patients and methods

All physicians in Sheffield's two major hospitals (the Royal Hallamshire and Northern General Hospitals) were asked to report any patients with proved or suspected primary biliary cirrhosis who were alive at any time from 1 January 1977 to 31 December 1979. In addition all cases in which antimitochondrial antibodies had been reported by the immunology department at the Royal Hallamshire Hospital (the sole immunology laboratory for the city) were followed up by reference to the clinical records. The diagnosis of primary biliary cirrhosis was established on a combination of clinical, biochemical, serological, and histological criteria as defined by Klatskin and Kantor.[1] Liver biopsy results were available for all patients except two elderly women in whom the procedure could not have been ethically justified but in whom all other features were entirely consistent with the diagnosis. Three patients died before the histological diagnosis was established, but necropsy material was available. All the other data in this paper were derived from interviewing the remaining patients, specifically for this project.

The interview was to confirm that the clinical spectrum of the patients under study was comparable with that reported elsewhere for primary biliary cirrhosis and also to examine any possible environmental, genetic, and social characteristics. The study was restricted to patients living within the city boundary since areas adjacent to the city lay within the catchment areas of other hospitals.

Information on the population distribution within the city was obtained from the 1971 census. Data on the water supply to domestic households was provided by the Yorkshire Water Authority (Southern Division), which also provided information on the water analysis of the reservoirs supplying the city, based on regular routine checks. Further analysis of reservoir water for specific trace elements was carried out by Dr D R Ineson of the Department of Geology, Sheffield University, by atomic absorption spectrophotometry using both flame and heated

graphite atomic techniques. Antimitochondrial antibodies were measured by indirect immunofluorescence using a rat kidney as the tissue substrate and polyvalent FITC conjugated swine antihuman immunoglobulin (Nordic Immunochemicals, Tilburg).

Results and comment

Thirty-four patients were identified as having primary biliary cirrhosis during the period under study. The population of Sheffield is 520 000, and during the three years of the study nine new cases were identified. This gives an annual incidence of 5·8 per million population. Twenty-eight patients with established primary biliary cirrhosis were alive on 31 December 1978 and the same number (although not all the same patients) were alive on 31 December 1979, giving a point prevalence for both dates of 54 per million. Thirty-one patients were alive at some stage during the year 1979, a period prevalence for the year of 59 per million.

The survey included only two men, the overwhelming female preponderance being consistent with other reports. The mean age at diagnosis was 58·8 years (34-79 years). Thirteen of the 34 patients were aged over 65 years. This was a higher percentage of elderly cases than is usually reported and probably reflected the general reluctance of physicians elsewhere to refer their older patients to specialist centres. The presenting features were typical of the disease, being pruritus (nine patients), abdominal pain (six patients), jaundice (six patients), anaemia (four patients), and ascites (one patient). In eight patients the diagnosis was established after chance observations (either incidental abnormalities on physical examination or the unexpected finding of abnormal liver function values, in particular a raised alkaline phosphatase value). Five of these patients subsequently developed symptoms attributable to primary biliary cirrhosis (three ascites and two pruritus), leaving only three truly asymptomatic patients. Table I shows the frequency of relevant symptoms and signs and biochemical and serological abnormalities in the 34 patients. Serum alkaline phosphatase values were raised in all patients, although in one they returned to normal for six months. Antimitochondrial antibodies were found in 33 patients, the single exception being a woman who had all the other classical features of primary biliary cirrhosis. In 30 patients the autoantibody was consistently positive, while in two it was intermittently positive and in one it disappeared for almost two years after being present on several occasions (this was not the same patient as the one who had normal alkaline phosphatase values). The antimitochondrial antibody was found in a titre of at least 1/80 in all patients and in half it was detectable in a titre of equal to or greater than 1/1000. The diagnosis was supported by histological findings in all patients who underwent biopsy, though in many cases the diagnoses were

TABLE I—*Frequency of relevant signs and symptoms and laboratory values in patients with primary biliary cirrhosis*

Clinical features	No of patients	Laboratory values	No of patients
Pruritus	25	Raised bilirubin (≥17 μmol/l)	26
Jaundice	12	Raised alkaline phosphatase (>100 IU)	34
Xanthelasma	7	Raised IgG (>16 g/l)	11
Pigmentation	8	Raised IgA (>4 g/l)	9
Hepatomegaly	26	Raised IgM (>2 g/l)	24
Splenomegaly	16	Antinuclear antibody (≥1/20)	5
Oedema/ascites	13	Antimitochondrial antibody (≥1/80)	33

Conversion: SI to traditional units—Bilirubin: 1 μmol/l ≈ 0·06 mg/100 ml

"consistent with" rather than "diagnostic of" primary biliary cirrhosis. The diagnoses were based on six surgical and 50 percutaneous biopsies.

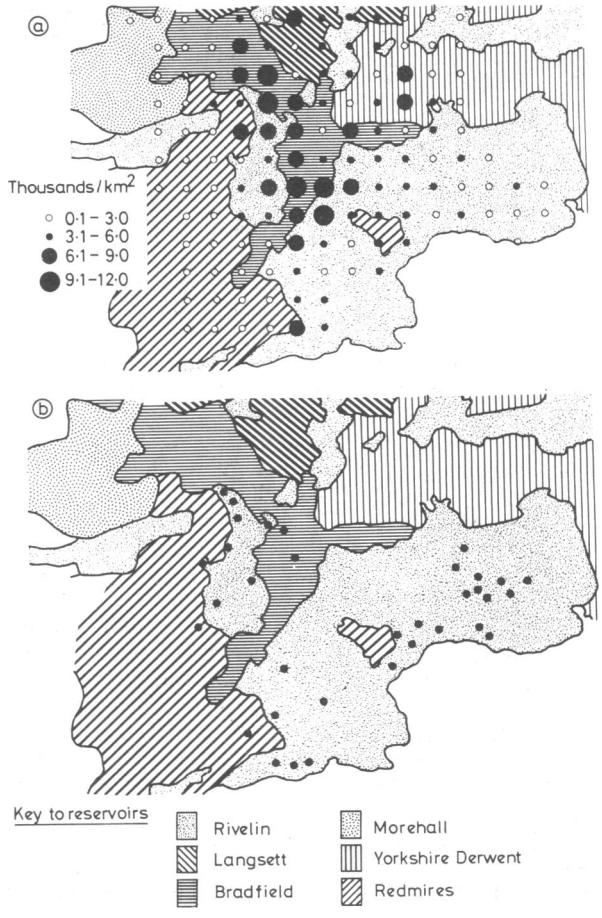
During the study it became apparent that the distribution of cases throughout the city did not correspond to the population density (see figure), and there was suggestion of possible clustering in certain areas. These areas did not share any geographical peculiarities, nor were the patients confined to any socioeconomic groups. None of the patients were known to be related, and careful questioning failed to reveal any suggestion of familial disease.

For historical and geographical reasons the city of Sheffield has a complicated domestic water supply, obtaining its water from several reservoirs. Analysis of the patients' homes with reference to the water supply showed that 30 of the 34 patients received their domestic water from a single reservoir (Rivelin). When the population supplied by each reservoir was taken into consideration, it was clear that the

TABLE II—*Prevalence of primary biliary cirrhosis according to water supply*

Reservoir	% of city population served by reservoir	% of cases of cirrhosis	Period prevalence* (per million)	Point prevalence‡ (per million)
Rivelin	40	88	144·0†	115·4†
Langsett	20			
Bradfield	15	6		
Morehall	10		12·5	12·8
Yorkshire Derwent	7			
Redmires	7	6		
Total	99	100	65·4	53·8

*Over three years; † (Rivelin *v* other reservoirs) $p < 0.001$ (comparison of 2 Poisson means); ‡On 31 December 1979.



Map of Sheffield city showing (*a*) distribution of population and (*b*) distribution of cases of primary biliary cirrhosis according to water supply.

prevalence of primary biliary cirrhosis in the area supplied by this reservoir was more than 10 times that supplied by the other reservoirs (table II; $p < 0.001$, using comparison of two Poisson means[3]). Since only four cases of primary biliary cirrhosis were found in the rest of the city, comparative figures on each separate reservoir were meaningless.

In an attempt to discover any difference between water from Rivelin and that from the other reservoirs chemical analyses of the water were performed. Table III summarises the findings, which showed no significant relevant differences apart from the water hardness (both total and non-carbonate) and fluoride levels. Although most of the water supplying the city was unusually soft, that from the Rivelin reservoir was particularly so. The fluoride content of the water in the Rivelin reservoir water was lower than that of any other reservoir ($p < 0.05$).

The assumption that domestic water supply played any role in the development of the liver disease would be valid only if patients had lived in the same area for many years since (*a*) many patients alive at the time of study had been diagnosed before 1977, and (*b*) when diagnosed clinically many patients had advanced disease which had obviously been present in a subclinical form for several years. All

TABLE III—*Comparison of water hardness and fluoride levels in Sheffield reservoir water. Values are means ± SD*

	Rivelin	Bradfield	Redmires	Yorkshire Derwent	Morehall	Langsett
Total hardness* (mg/l)	38·9 ± 3·8	45·9 ± 4·2	43·0 ± 8·0	91·5 ± 10·7	41·3 ± 4·3	44·4 ± 6·7
Non-carbonate hardness* (mg/l)	28·1 ± 3·4	37·6 ± 4·5	33·3 ± 4·6	62·6 ± 11·8	32·7 ± 5·4	31·0 ± 5·8
Fluoride† (mg/l)	0·067 ± 0·012	0·095 ± 0·013	0·142 ± 0·025	0·098 ± 0·013	0·084 ± 0·013	0·093 ± 0·013

Chemical analyses showing no difference in relation to Rivelin water: NH_4,* NO_2,* NO_3,* pH,* SO_4,* SiO_2,* Na,* Mg,† Al,† P,* Cl,* K,* Ca,* Mn,* Fe,* Co,‡ Cu,† Zn,† Mo,‡ Cd.‡
*Mean of 240 estimations on each reservoir (1974-9); †mean of 30 estimations on each reservoir (1977-9); ‡single estimation (August 1979).

except eight patients had lived all their lives in Sheffield. Those born outside the city had spent 31 to 67 years (mean 49 years) in the city before presentation. The average length of time spent in the same house was 20·1 years (range 1-50 years), and the average time spent in the same area (postal district) was 29·3 years (range 2-72 years). The mean period of residence in an area supplied by the same reservoir was 42·0 years (median 35 years, range 2-77 years).

Discussion

This study seems to have uncovered two features about the epidemiology of primary biliary cirrhosis. Not only has it shown a surprisingly high prevalence of the disease within the city of Sheffield but it has also highlighted great differences in prevalence between various parts of the city. The importance of the first conclusion is difficult to assess since there is little published data available on the prevalence of the disorder elsewhere. Nevertheless, the point prevalence of 54 cases per million here compares with a reported prevalence of 18 per million in Edinburgh.[4] The clinical and laboratory investigations were comparable with those reported in other studies, suggesting that the condition these patients had was indeed primary biliary cirrhosis and not some other liver disorder. Although about a quarter of the patients were detected at a presymptomatic stage, all but three later developed symptoms. Reviewing the laboratory reports for positive antimitochondrial antibodies served as a useful means of identifying cases for the survey, but only one patient was discovered in whom the diagnosis had not already been established. There is therefore nothing to suggest that the high prevalence is due to unusually intensive investigation of the population. The figure may indeed be an underestimate since it is impossible to assess how many other asymptomatic cases remain undiagnosed. Patients are unlikely to have been lost out of the city boundary since the Sheffield hospitals serve as referral centres and few if any patients are referred out of the city for diagnosis.

The second observation—namely, the apparent clustering of cases in certain parts of the city—requires another explanation. There is no evidence that the clustering is due to familial aggregation. Familial primary biliary cirrhosis is rare,[5-7] careful questioning failed to reveal any relationship between the patients, and examination of HLA types (unpublished observations) has not shown any association.

The possibility that the clustering may have reflected selective referral patterns seems unlikely since an analysis of all patients under hospital care with a diagnosis of chronic active (lupoid) hepatitis showed a geographical distribution corresponding closely to the population distribution within the city. All physicians responded to the request for information about cases of primary biliary cirrhosis, effectively excluding the possibility that the geographical distribution reflected non-response by some colleagues. It remains impossible, however, to exclude differences due to variation in diagnostic acumen between one physician and another.

Although other hitherto undefined factors may be responsible, the association between a common water supply and the clustering appears striking. The idea of an environmental factor in the cause of primary biliary cirrhosis is not new. Douglas and Finlayson[7] reported the disease in a mother, daughter, and friend and suggested that the condition may result from the exposure of a genetically susceptible individual to a particular environmental factor. If there is some factor related to the domestic water it is reasonable to suppose that many years of exposure would be required to induce chronic liver disease, since patients with primary biliary cirrhosis often present clinically with advanced liver damage. The data presented here show that the stability of the population in Sheffield would be consistent with such a hypothesis.

What is the nature of the factor in the water? Much interest has been shown in the trace metals copper and zinc since both have been reported in unusual amounts in the livers of patients with primary biliary cirrhosis.[8 9] Analysis of water samples from the reservoirs supplying Sheffield showed no increase in either of these trace elements in water from the Rivelin reservoir. Indeed, analysis of water for a much wider spectrum of materials has so far shown no striking differences in the water, although the water from Rivelin appears to be particularly soft and the fluoride concentration is lower than in any of the other reservoirs. Neither of these differences is particularly spectacular, and it is difficult to see how either could be directly implicated in the pathogenesis of primary biliary cirrhosis. Nevertheless, contamination may occur between the reservoir and the domestic taps, which may lead to other materials being ingested by the patients. Copper piping is found extensively throughout the city, and preliminary analysis of water taken at random from the homes of patients and controls has shown as much as a three-hundred-fold variation in copper concentration from one house to another in both groups. A wide range of other substances, both organic and inorganic, may be implicated.

Sheffield is an industrial city in which many different processes using a wide range of elements are found. The possibility that the environmental factor could be related to atmospheric pollution is ruled out by the patchy distribution of the clusters of cases. With a prevailing westerly wind it is inconceivable that any pollutant could spare the centre of the city. There is a large copper smelting works in Sheffield but this is located in an area with no cases of primary biliary cirrhosis lying to the east of one cluster and the north of another.

Bone disease and encephalopathy related to haemodialysis for chronic renal failure has been reported in Sheffield and its relationship to water aluminium has been well documented.[10] Although aluminium concentrations are high in the Rivelin reservoir, they are also raised in two other reservoirs supplying the city, thereby making it unlikely that this is the responsible factor.

Despite the possible incrimination of the water supply, it seems likely that other factors must be important. Even in the high-prevalence area the prevalence of primary biliary cirrhosis is 1 in 7000 and the predilection for women as well as the occurrence of familial cases elsewhere remains to be explained. Possibly there are genetically predisposed individuals (possibly definable by the presence of the antimitochondrial antibody) who may develop primary biliary cirrhosis if suitably exposed to the crucial environmental agent. The fact that the prevalence of the disease seems to rise with increasing age is further indirect evidence in support of an environmental factor.

The epidemiology of primary biliary cirrhosis has received scant attention in the past. Hamlyn and Sherlock[11] studied the

frequency and distribution of the condition in Great Britain by analysing death certificates in 1967-71. They could not define any regional variations. A major limitation of the survey was the fact that it covered a period when the diagnostic value of the antimitochondrial antibody was not widely established. The authors conceded that their study may not have been representative in that they reported a predominance of patients in social classes I and II, whereas in this study the distribution of the disease more closely paralleled the distribution of social classes in the community. Much more information is needed on the epidemiology of this disorder in this country and elsewhere in the world, both to confirm the regional variation and to test the hypothesis of an environmental agent. Indeed, further studies along these lines might provide clues to the cause of this puzzling disorder.

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Cimetidine and ranitidine: comparison of effects on hepatic drug metabolism

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Summary and conclusions

Paired studies of hepatic microsomal function were conducted in eight subjects during treatment with two histamine H_2 antagonists, cimetidine and ranitidine. Cimetidine but not ranitidine inhibited the metabolism of antipyrine (phenazone) and demethylation of aminopyrine (aminophenazone) as measured by breath $^{14}CO_2$ production after intravenous injection of ^{14}C-aminopyrine.

These results suggest that the metabolic inhibitory actions on the liver may be separated from H_2 antagonist effects, and that ranitidine has an advantage over cimetidine by not inhibiting microsomal drug oxidative function.

Introduction

When drugs such as warfarin, antipyrine (phenazone), and diazepam are taken with cimetidine their metabolism is retarded.[1 2] This interaction has been attributed to the imidazole ring structure of cimetidine.[1] Many imidazole compounds inhibit hepatic mono-oxyxgenase function,[3] and in the case of cimetidine this effect may be mediated in part through direct binding to microsomal cytochrome P450.[4] Ranitidine is a new potent H_2-receptor antagonist.[5] The central imidazole group has been replaced by a furan ring and the side chain has been modified. We have compared the effects of therapeutic doses of cimetidine and ranitidine on hepatic microsomal function.

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Subjects and methods

Eight subjects (six healthy volunteers and two patients with duodenitis) were studied after the nature and purpose of the investigation had been explained and after approval had been obtained from the hospital ethical committee. Antipyrine clearance was measured in all eight subjects and ^{14}C-aminopyrine (^{14}C-aminophenazone) breath analysis conducted in six subjects before and during treatment with cimetidine 1 g daily and ranitidine 200 mg daily. The studies were performed in a cross-over fashion. Five subjects took cimetidine followed by ranitidine, the remainder ranitidine followed by cimetidine. Cimetidine was given for one to six weeks, and ranitidine for one week only (see table).

Antipyrine (15 mg/kg) was taken by mouth during fasting and saliva collected at intervals from three to 24 hours afterwards. Antipyrine concentrations were measured spectrophotometrically[6] and the half life and metabolic clearance rates calculated from the semi-logarithmic plot of salivary concentration against time.

^{14}C-AMINOPYRINE BREATH ANALYSIS

The procedure was as described.[7] All studies were performed on fasting subjects. After intravenous administration of 2 μCi ^{14}C-aminopyrine, 2 mmol* exhaled carbon dioxide was trapped in a